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Are nutrition-induced epigenetic changes the link between the socio economic pathology and cardiovascular diseases?

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Abstract

The prevalence of cardiovascular diseases (CVD) and diabetes mellitus type 2 (DM 2) is decreasing in developed countries, despite the increase in the percentage of subjects with obesity and other well recognized cardiovascular risk factors. In contrast, the recent transition of the economic model experimented by developing countries, characterized by the adoption of a western lifestyle, that we have denominated socio-economic pathology, has led to an increase in the burden of CVD. It has been demonstrated that conventional cardiovascular risk factors in developed and developing countries are the same. Why then does population of developing countries have nowadays, a higher incidence of cardiovascular disease than those of developed countries, if they share the same risk factors? We have proposed the existence of a higher susceptibility to the development of systemic inflammation at low levels of abdominal obesity (AO) in population of developing countries and consequently endothelial dysfunction, insulin resistance, DM 2 and CVD. In contrast, an important percentage of obese people living in developed countries have a healthy phenotype and low risk of developing CVD and DM 2. Human epidemiological studies and experimental dietary interventions in animal models have provided considerable evidence to suggest that nutritional imbalance and metabolic disturbances early in life may later have a persistent effect on the adult's health that may even be transmitted to the next generations. Epigenetic changes dependent on nutrition could be the key in this evolutionary health behavior, acting as a buffering system permitting the adaptation to environmental conditions by silencing or increasing the expression of certain genes.

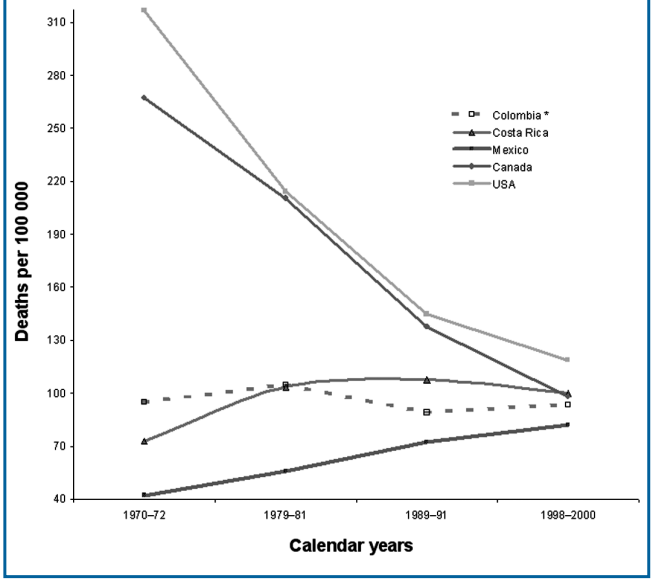
Key words: obesity, metabolic syndrome, epigenetic, adaptive response, socio economic pathology.

Introduction

Worldwide, cardiovascular diseases (CVD) are the leading cause of death. It is calculated that 3.8 million men and 3.4 million women die each year of this cause [1]. Moreover, an increase from 47 million disability-adjusted life years in 1990 to 82 million, is globally projected for 2020 [2]. Although age-adjusted cardiovascular death rates have declined in several developed countries, rates of CVD have greatly risen in low and middle-income countries, with about 80% of the burden now occurring in the latter [3]. It has been estimated that 5.3 million deaths attributable to CVD occurred in developed countries in 1990, against 8 to 9 million in developing countries[4]. In USA, between 1972 and 2002, the CVD death rate declined by 54%, specially due to the decline in coronary heart disease (CHD) and stroke mortality (62%[5]).

In contrast, in Colombia, the death rate for CHD in 20-84 year old subjects increased from 58.5 per 100.000 in 1980 to 103.2 in 1996. Only 30% of this increase could be attributed to population aging[6]. From 1997 to 2001 acute myocardial infarction (AMI), stroke and diabetes mellitus type 2 (DM 2) were responsible for 213.150 deaths (19.6%). Together, these deaths exceeded those due to violent causes, which for several years were the first cause of death in this country (Figure 1).

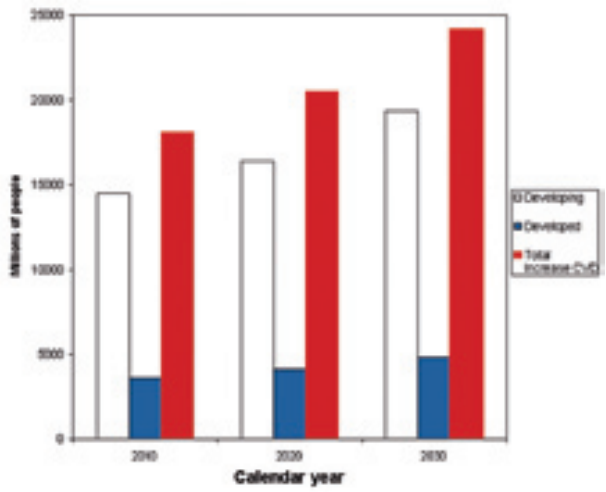
Figure 1. Trends in death certification rates per 100.000 inhabitants for coronary heart diseases in 5 countries of the Americas in different stages of development 1970–2000



Adapted from Rodriguez T, Malvezzi M, Chatenoud L, Bosetti C, Levi F, Negri E, La Vecchia C. Trends in mortality from coronary heart and cerebrovascular diseases in the Americas: 1970-2000; Heart. 2006 Apr;92(4):453-60

In the last years the transition in life style experimented by developing countries due to the adoption of a western economic model, with an increased exposure to risk factors such as high saturated fat diets, sedentarism, psycho-social stress and cigarette smoking has led to an increased prevalence of obesity, alteration in lipid profile, in plasma glucose and high blood pressure[7] which could explain in part the CVD epidemic observed in those countries (Figure 2). We have proposed that the recent exposure to these changes determines a higher degree of biological bad adaptation which entails a greater risk of CVD. The shorter the exposition to the new lifestyles, the less the biological adaptation and the higher the risk of CVD. We have proposed to call this process socio-economic pathology, to express the interaction of socio-economic factors and classic cardiovascular risk factors with the length of time of exposition of a particular society to the western lifestyle[8].

Figure 2. Projected annual trends in CVD deaths in populations at different stages of development 2010–2030



Adapted from Mackay, J; Mensha, G, A; World hearth organization (WHO), Center for Disease control (CDC)¨ The atlas of heart disease and stroke¨ the future and the past;(CDC).

Cardiovascular risk factors in developing countries

A large study realized in Brazil identified that conventional cardiovascular risk factors such as hypercholesterolemia, smoking, hyperglicemia and obesity are associated with AMI in this population[9]. The INTERHEART study[10] identified the risk factors associated with AMI in 52 developed and developing countries. Smoking, hypertension, abnormal lipids, abdominal obesity (AO), diabetes and psychosocial stress were associated with ischemic disease in all regions of the world with no differences in age and gender. However, Lanas et al.[11] reported the results from 1237 Latin American subjects from Brazil, Argentina, Chile and Colombia, included the INTERHEART study, demonstrating that central obesity was the most important risk factor associated with AMI in this population, much more than in the entire population of the study. We believe that the biological response to obesity in developed countries is different than in developing countries, and that this response is modulated through epigenetic regulation.

Is Population from developing countries more susceptible to the inflammatory effect of abdominal obesity?

The relationship between obesity and incidence of CVD was established several years ago. The Framingham cohort demonstrated that obesity is an independent predictor of CVD in both sexes[12]. This relation became more evident in subsequent studies[13]. The IDEA study, realized in 63 countries with 170.000 subjects in primary care, concluded that for an increase of 14 cm in waist circumference for men and of 14.9 cm for women, the probability of CVD rose by 21% to 40%[14]. Two cohort studies performed in Korea[15] and United States[16], established

that not only is obesity but also overweight the main risk factors associated with the risk of death, in subjects that have never smoked.

The National Cholesterol Education Program Adult Treatment Panel III (NCEPT-ATP III) recognized overweight and obesity as major underlying risk factors for CVD, AO being more highly correlated with CVD than body mass index[17].

The International Diabetes Federation (IDF) established the presence of AO as an obligatory criterion for the diagnosis of metabolic syndrome (MS), which is strongly related with the development of DM 2 and CVD. Moreover, the IDF has proposed a different threshold for waist circumference depending on regions and ethnic groups[18]. In the Andean population with no previous CVD history, our group reported that criteria for MS proposed by IDF is more useful to identify subjects with MS than ATP-III criteria[19].

In addition, several studies carried out in developing countries have reported lower waist circumference cut-off points associated with cardiovascular risk than those reported in developed countries. Misra et al [20], reported higher risks of cardiovascular events among Asian Indians with waist circumference of ≥90 cm and ≥80 cm for men and women, respectively. Similar results have been obtained in Latin American countries[21; 22]. In healthy young Colombian men a waist circumference of 88 cm identified subjects in cardiovascular risk with a sensitivity of 83.7% and a specificity of 84.8%[23]. In Ecuador, it was demonstrated that a waist circumference of 90 cm in men is the best cut-off point associated with the presence of at least two other MS criteria according to the NCEPT-ATP III[24].

The study Abdominal Obesity as a Risk Factor for Coronary Artery Disease, (ABOCAD) performed in Colombia, demonstrated that a waist circumference of 94 cm for men and 84 cm for women is an independent risk factor associated with coronary artery disease, defined as at least a 50% reduction of the internal diameter of the secondary coronary arteries or a 30% reduction of the main coronary arteries.

Waist circumference has demonstrated to be an easier parameter to evaluate the content of visceral fat, which is the main source of pro inflammatory cytokines[25,27]. These adipokines are elevated in serum of obese subjects [28] and it has been proposed that the systemic inflammation produced by the adipose tissue participates in all stages of the development of atherosclerosis such as endothelial dysfunction[29], atheroma formation, rupture of plaque and acute thrombotic complications[30]. C-reactive protein (CRP), produced by the liver in respond to the stimulus of tumor necrosis factor alpha (TNFα) and interleukin-6 (IL-6) are increased in subjects with multiple acute coronary events and are a strong independent predictor of new acute coronary events[31]. We have demonstrated in the Andean region that CRP is an independent risk factor for essential hypertension[32] and pregnancy induced hypertension[33,34]. Moreover, the concentration of CRP, IL-6 and TNFα are increased in dislipidemic subjects with MS [8; 35] and in overweight and obese children[36]. Regardless of the differences in the methods to quantify these inflammatory markers we have observed that in general the concentration of the proinflammatory cytokines is higher in our population than that reported in the population of developed countries [8]. For this reason we have proposed that the systemic inflammation associated with AO is increased in population of developing countries at lower levels of AO. Further cohort studies in developing countries with the enrollment of a large population are necessary to confirm this proposal, and whether the population of these countries has a major risk of developing atherosclerosis and CVD with lower levels of AO[37].

The obese metabolically healthy: An observation of developed countries

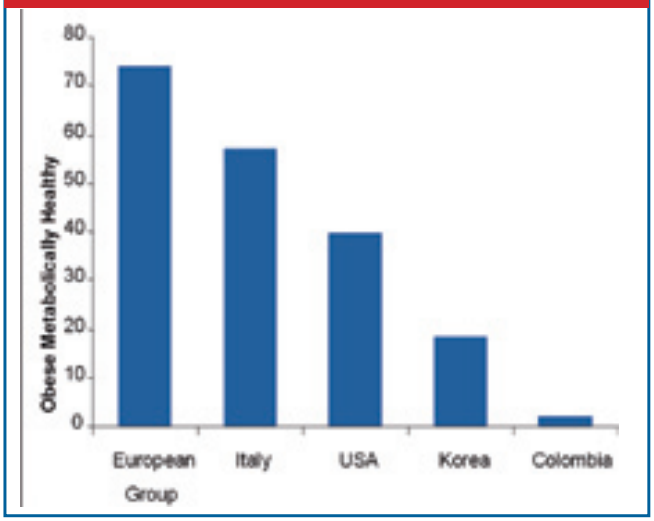
Abdominal obesity has been found to have a major correlation with a cluster of diabetogenic, atherogenic, prothrombotic and metabolic abnormalities[38]. Obesity is strongly associated with other chronic metabolic diseases and insulin resistance[39]. However, a subset of obese subjects that have a low risk of developing CVD has recently been reported. These subjects, termed obese metabolically healthy (OMH) despite the increase in fat tissue, have a healthy metabolic profile, including normal insulin sensitivity[40]. Several large studies performed in developed countries have demonstrated a high prevalence of obese subjects without insulin resistance (IR)[41,43]. Ferranini et al[41] enrolled 1146 Caucasian men and women whose insulin resistance (or sensitivity) was measured by the euglycemic insulin clamp technique. Only 26% of all obese individuals with any metabolic disorder were IR. Another large study[42] performed in Italy evaluated insulin sensitivity using the homeostasis model assessment (HOMA), demonstrating that 57% of the obese subjects were healthy and showed no IR. McLaughlin et al. reported that 30% of 465 apparently healthy individuals had normal insulin sensitivity, though either overweight or obese[43].

Subsequently small studies[44-46] performed in USA, Canada and Korea have reported a 20 to 40% prevalence of OMH women. The healthy metabolic profile in these obese women is characterized by normal blood pressure, high level of high density lipoprotein (HDL)-cholesterol, low levels of fasting triglycerides, normal fasting insulin and fasting glucose, as well as normal insulin sensitivity[44,45]. In addition, it was demonstrated that these healthy and obese women

had significantly less visceral fat (as measured by computed tomography) and lower levels of CRP, IL-6 and oxidized LDL than women metabolically abnormal[45;46]. These differences were not significant anymore after CRP levels were adjusted for the content of visceral fat[46]. We can speculate that OMH showed a healthy profile due to a special phenotype that expresses less or smaller visceral adipocytes, which are less proinflammatory and metabolically active. In support of this proposal, some studies have demonstrated that the growth of adipocytes is associated with substantial changes in metabolic functions such as cholesterol metabolism[47] and response to insulin[48]. In addition it has been demonstrated that hypertrophic adipocytes produce an important systemic inflammation[49], increasing the risk of metabolic and cardiovascular complications[50;51]. Thus, the lower proinflammatory activity of the adipocytes in OMH individuals might confer a lower risk of CVD. Recently, in a study done in Canada[52] with a cohort of 1824 non diabetic men, free of ischemic heart disease (IHD) that were followed for a period of 13 years, obesity per se didn't increase the risk of IHD, but did so when IR was present. This result suggests that IR is a key element to increase the risk of CVD in obese subjects. In the absence of IR obese subjects don`t have an increased risk of CVD.

The studies currently published on OMH subjects have been carried out in developed countries. In Colombia, in a sample of 579 abdominal obese subjects according to IDF criteria, we identified only 1.7% of individuals with AO and without IR. The other 98.3% of subjects met all the criteria for MS. This result supports the proposal that the population of developing countries, due to biological adjustment for the recent changes in its life style imposed by the economic western model, has become prone to develop IR, and the visceral fat prone to produce a systemic inflammatory response. On the other hand, populations of developed countries with a longer exposure to western life style have developed mechanisms of adaptation associated with the presence of visceral adipocytes that secrete anti-inflammatory citokynes, such as adiponectine, a substance which maintains an adequate sensibility to insulin, thus contributing to a smaller number of obese subjects with IR and a higher number of OMH subjects (Figure 3). Large prospective studies will be necessary to confirm this hypothesis although some already published data from developed countries support this proposal. Brochu et al[44] evaluated the presence of IR in obese postmenopausal women. The authors employed a multiple regression analysis to identify independent factors that distinguished OMH subjects from those with abnormal metabolic profile. The major independent factor was low amounts of visceral adipose tissue. Interestingly, 13% of the variation observed in the normal insulin sensitivity was an earlier age-related onset of obesity (between 13-19 years of age). This finding is in line with the results reported by Muscelli et al.[53] who observed that in obese subjects with preserved glucose tolerance, the relationship between the duration of obesity and the insulin sensitivity was directly proportional, irrespective of the degree of obesity. Moreover, in a longitudinal study realized in a developed country,it was demonstrated that gain weight during childhood was associated, contrary to expected, with reduced risk of CHD in adulthood[54]. Globally, these results suggest that human beings develop an adaptive response to new environmental and nutritional conditions and that this response is dependent of the time that a determinate society has been exposed to the new conditions.

Figure 3. Prevalence of obese subjects metabolically healthy



Adapted from: Ferrannini et al. J Clin Invest 1997; 100:1166-1173. Bonora et al. Diabetes 1998; 47:1643-1649. Brochu et al. J Clin Endocrinol Metab 2001; 86:1020-1025. Shin et al. Int J Obes (Lond) 2006; 30:1529-1534.

What are the mechanisms of the adaptive process?

Most living organisms acquire tolerance when they are exposed to subletal environmental alterations[55]. When this behavior is used to protect the tissues it is named preconditioning (PC). This response is observed in a vast variety of species from bacteria to mammalian cells. For example, the ischemic preconditioning, protects the brain cells from ischemic damage provoked by prolonged ischemia[56]. In the heart, transient ischemia induces myocardial protection against subsequent ischemia and reperfusion injury[57].

It has been proposed that the heart possesses an ability to adapt to stress by changing its phenotype, making it more resistant. There are evidences of adaptation of the heart to brief coronary stress (ischemic, exercise, heat stress, rapid ventricular pacing and other types of stress). Moreover, it was found that PC is a biphasic phenomenon that protects in the early stage of the stress against myocardial infarction and in the later phase, against myocardial infarction and myocardial stunning[58].

In fact, PC is the result of a cascade of cellular events, that activates an ¨alarm system¨ against an imminent injury, and induces a defensive phenotype that represents a complex response requiring synchronized activation of several genes[58].

It is interesting to speculate that the phenomenon of PC could explain the inverse relationship between the number of obese people and CVD in developed countries: the prevalence of obesity increases but the cardiovascular mortality decreases[1-7; 59]. In addition, it has been proposed that one of the reasons for the increase in life expectancy is that our genome permits adaptation to different conditions and environments[60]. Although genetic factors might predispose to CVD, not all people genetically predisposed develop it, which suggests that there are environmental factors that regulate this relationship[61-65]. Moreover, the World Heart Organization reported that 80% to 90% of people dying from coronary heart disease have one or more major risk factors influenced by their lifestyle[1].

Nutrition induced epigenetic changes: the situation in developed countries

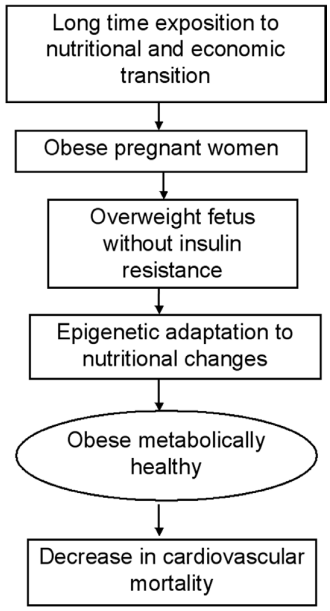
Populations all over the world are permanently exposed to changes in food intake from conception to death. Several decades ago it was proposed that a genetic component could be responsible for differences in dietary response[61]. Recently the interaction between nutrition and gene expression has been examined[61-63]. Dietary habits represent a key environmental factor that modulates gene expression throughout life[64]. Therefore, a better understanding of the interaction of genetic and environment in the association between CVD and insulin resistance could help to prevent MS and CVD[65;66]. Epigenetic is the science that explains the variation of genes expression in response to changes in environmental conditions[64]. This term includes any process that alters gene activity without changing the DNA sequences, and leads to rapid modifications that can be transmitted to daughter cells, although, some epigenetic changes can be reversed[65]. Epigenetic modulation of gene expression serves as a defence mechanism against harmful agents, so that genes can be silenced or expressed by various types of epigenetic processes such as methylation and acetylation[66]. DNA methylation is the process whereby an area of a chromosome known to be a regulatory region for a specific gene is methylated, process that inhibits the gene expression and consequently isn't transcribed into messenger RNA. Another epigenetic process is chromatin modification. Chromatin is the nuclear complex consisting of DNA wrapped around histone proteins which can be modified by substances such as acetyl groups (acetylation) and enzymes to influence gene expression[67].

Cooney et al.[68] reported that a diet supplemented with methyl donors in pregnant mice influences epigenetic variation and DNA methylation of offspring, affecting their health and longevity. This result argues that an environmental stimulus early in life can change the stable expression of genes and affect the phenotype of the adult.

Actually, it is not yet clear what is the participation of epigenetic in the physiopathological mechanisms of IR and MS. However, there is available information about how maternal diet or other in uterus/postnatal exposure may "program" susceptibility to later development of CVD in adulthood. There is no doubt that the exposition to harmful agents during pregnancy makes that living beings adopt several strategies to optimize their chances of survival, using genetic plasticity[69;70]. When the environment change becomes a permanent and transgenerational condition, living beings must create new strategies to guarantee their survival. We believe that it is the case of the OMH. There is not much available information about the theory that populations that are exposed for several generations to fat rich diet or to junk nutrition and obesity, acquire with time adaptive mechanisms that provide cardiovascular protection. In a study where pregnant sows were fed a standard gestational diet or an atherogenic gestational diet and their offspring maintained on either a standard diet or an atherogenic diet until the pubertal age (5 months), all offspring that received atherogenic diet had greater serum cholesterol concentration and aortic fat deposition compared with those on the standard diet. However, piglets from sows fed a standard diet that in postnatal life were fed an atherogenic diet, were the only ones that developed early coronary atherosclerosis, whereas those prenatally exposed to the fat diet and maintained on the same diet had no evidence of aortic lesions despite being hypercholesterolemic[71]. In another study, rats were fed a fat rich diet or normal chow throughout pregnancy and lactation. The vascular function was assessed at 180 days of age in mesentery arteries using endothelium-dependent dilation to acetylcholine. The offspring of fat fed dams raised on the same diet conserved the endothelial function and had lower heart rate in comparison with offspring of standard diet dams raised on the same diet or with offspring of fat fed dams raised on standard diet. However, the early and continue exposition to a fat diet in one generation does not prevent the increase of blood pressure[72]. Gallou-Kabani, et al.[73] evaluated in rats, the transgenerational effect of obesity and nutrition. The second generation of female rats, from obese mothers that were exposed to a high fat-diet at 1 month of age, developed a resistance to a high fat-diet at 6 months of age, characterized by complete protection against hyperglycemia, obesity and hyperinsulinemia but incomplete protection

against hypercholesterolemia. These experimental works are reflecting some of the data observed in the human OMH. More studies are necessaries to fully understand the process involved in the epigenetic adaptation induced by nutrition that results in an OMH (Figure 4).

Figure 4. The effect of enviromental factors in the development of cardiovascular diseases and related conditions in developed countries



Nutrition induced epigenetic changes: the situation in developing countries

In rodents, maternal dietary restriction (i.e. low protein diet) or high fat over-feeding during pregnancy or/and suckling period, gives rise to an offspring phenotype predisposed to the development of adulthood CVD[74]. This phenotype may include some components of MS such as: high blood pressure, abnormal serum lipid profiles, increased adiposity, hyperinsulinemia, abnormal glucose homeostasis, endothelial dysfunction and atherosclerosis[75,82]. Moreover, maternal diet manipulation in rats produces disturbances in the development of the endocrine pancreas[83,87]. Poor development of the pancreas and IR as a response to intrauterine malnutrition may be useful for survival in early life; however it may become a risk factor for glucose intolerance and diabetes in adulthood[88-90].

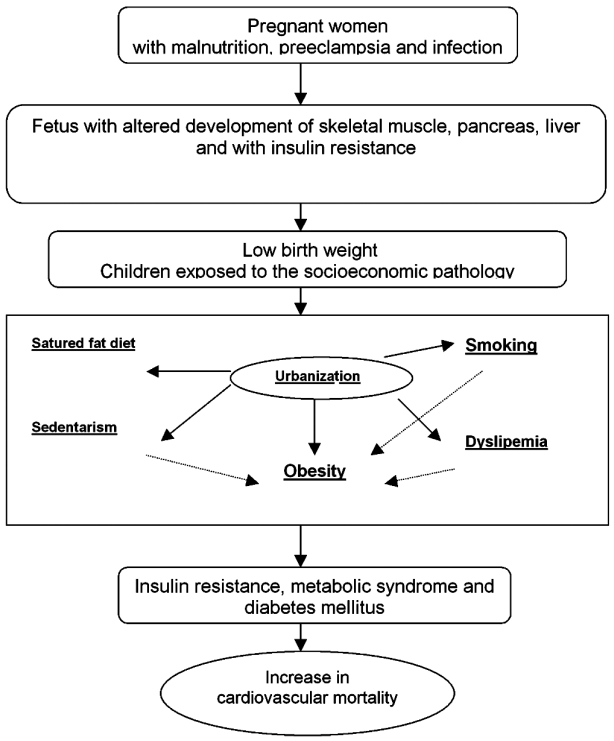
B-cells mass is decreased in rats´ offspring exposed to a low protein diet associated with an increase of apoptotic rate and a reduction of islet cell proliferation, along with an alteration in the development of islet blood vessel[83,88]. Impaired pancreatic β-cells development may cause a lasting reduction in the insulin-secretor response. However the exhaustion of the low β-cell mass may only be clearly revealed when the insulin produced by the pancreatic β-cells is not enough to maintain a normal glucose homoeostasis. Aging, obesity or pregnancy augments insulin demand, increasing the risk of hyperinsulinism, IR and DM 2[88,90].

Epidemiological studies and clinical observations have permitted to understand the relationship between under nutrition during fetal life and chronic diseases in later life. Low birth weight has been linked to adulthood heart disease, hypertension, DM 2, IR, vascular dysfunction, obesity and dyslipidemia[91,96]. A possible explanation of this phenomenon may be the thrifty phenotype hypothesis, proposed by Neel in 1962 in base of observations realized in developed countries after the second ward world[97]. This hypothesis proposed that, in response to a poor nutrition in intra uterus life, a predictive adaptive response is made by the fetus to maximize uptake and conservation of any nutrients available, resulting in a conservative metabolism with impaired growth of cells and organs. When the infant is exposed to a similarly deficient postnatal diet to that experienced in uterus, the programming of the thrifty phenotype confers a ´predictive adaptive´ advantage, since these individuals are then biologically prepared to withstand poor diet. The problem arises when postnatal diet is adequate or plentiful and exceeds the range of the predictive adaptive response[67,98].

Experimental models have shown that a poor fetal growth, followed by postnatal catch-up growth is associated with reduced average longevity in mice[99]. In humans, a longitudinal analysis performed in 3641 boys demonstrated, that the subjects with a low weight at birth who achieved an average or above average body mass at the age of 7 years on, had higher death rates from coronary heart disease[100]. Rapid weight gain in infants that were small and low weight at birth may lead to an unfavorable body composition with disproportionately high fat mass in relation to lean body mass, which could in turn lead to insulin resistance[101].

These studies support our proposal of the socio economic pathology as the cause of the epidemic of obesity, MS, DM2 and CVD in developing countries. Thus, this epidemic is associated with a recent socio economic and nutritional transition in a period of time not long enough to provoke an adaptive response and epigenetic changes to the excess of fat in the diet (Figure 5).

Figura 5. The effect of environmental factors in the development of cardiovascular diseases and related conditions in developing countries



Conclusions and hypotheses

Developing countries are nowadays going through the economic process and the changes in life style experimented few generations ago by developed countries. After several generations exposed to the harmful environment the population of developed countries has achieved epigenetic adaptation. This might be the explanation to the phenomenon of the OMH observed in an important percentage of obese individuals of developed countries. Comparative studies including population of developed and developing countries are necessary to understand better the different epidemiological behaviors observed in the CVD profile of populations with different lengths of time of exposition to new life styles.

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